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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/657,879	09/09/2003	Ronald G. Crystal	224325	2627

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EXAMINER	
ALONZO, NORMA LYN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/657,879	CRYSTAL ET AL.	
	Examiner	Art Unit	
	Norma C Alonzo	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 09/909/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 3-13 have been renumbered 2-12.

2. Claims 1-12 are pending and under consideration.

3. Claim 11 is objected to because of the following informalities: the statement "the flap is contact with" is inappropriately written. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 9, 11, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 7 directs to a method of increasing vascularity in a tissue flap, wherein the "rate of necrosis" in the tissue flap is decreased by contacting the tissue flap with the adenoviral vector. The term "rate of necrosis" of the tissue is indefinite as described because a skilled artisan is unable to determine the parameters defining "rate of necrosis." Specifically, there is no defined method or scale by which "rate of necrosis" could be measured. The specification does not clarify this statement; therefore Claim 7 is being indefinite.

4. Claim 9 directs to a completely "dissociated" tissue flap. This is an indefinite term because a skilled artisan is unable to determine the parameters defining "dissociated." Specifically, the term could direct to a tissue flap that is not connected to the host in any way or the term could direct to a tissue flap that is separated into smaller pieces, as in "dissociated tissue." The specification does not clarify this statement, therefore Claim 9 is indefinite.

5. Claim 11 directs to a tissue flap that is "substantially" cut away from the surrounding tissue. This is an indefinite term because a skilled artisan is unable to determine the parameters defining "substantially." Specifically, there is no defined

method of measuring the degree to which the tissue flap is cut away from the surrounding tissue. The specification does not clarify this statement, therefore Claim 11 is indefinite.

6. Claim 12 recites the limitation "re-association of the tissue flap" in the claim in reference to Claim 11. There is insufficient antecedent basis for this limitation in the claim. Claim 11 does not refer to any method of or action of "re-association."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Herlyn et al. (WO 98/39035; published September 11, 1998; filed March 6, 1998).

Claims 1-13 are directed to a method of increasing vascularity in a tissue flap wherein said tissue flap is injected with a replication-deficient adenoviral vector wherein said adenoviral vector comprises a nucleic acid sequence encoding an angiogenic factor wherein angiogenic factor is VEGF, $VEGF_{121}$, acidic fibroblast growth factor, basic fibroblast growth factor, alpha tumor necrosis factor, beta tumor necrosis factor, platelet-derived growth factor, or angiogenin wherein rate of necrosis in tissue flap is decreased

by contacting said tissue flap with said adenoviral vector whereby said nucleic acid sequence encoding the angiogenic factor is expressed in the tissue flap and vascularity in the tissue flap is increased.

Herlyn et al. teach a method for "increasing/inducing vascular development in mammalian tissue by delivering to the tissue a replication defective recombinant virus, preferably adenovirus, comprising a human growth factor gene under the control of regulatory sequences capable of directing expression of that gene in the tissue." (page 6, lines 1-7). It is noted that Claim 6 of Herlyn et al. recites that the tissue is skin, which will meet the limitation of being a tissue flap (see page 18, lines 3-18). Therefore, the invention of Claim 1 is anticipated.

The invention of Herlyn et al. also specifically provides "recombinant replication-deficient adenoviruses containing the selected growth factor gene, which permits expression of the gene products in mammalian, preferably human, skin." (page 11, lines 14-17). Therefore, Claim 2 is anticipated.

Herlyn et al. teach a method comprising administration of an adenovirus vector wherein "among the growth factors particularly useful in the present invention are vascular endothelial growth factors (VEGF)." (page 10, lines 4-5), with one of the genes administered to skin culture in the example method of the invention being $VEGF_{121}$ (page 10, lines 8-19). Therefore, Claim 3 is anticipated.

Further, Herlyn et al. teach a method for increasing vascular development in mammalian tissue comprising administration of an adenovirus vector wherein "the recombinant virus is injected intracutaneously or intradermally where the selected tissue

is skin." (page 14, lines 13-14). Further, in experiments in which human epidermal tissue was surgically grafted onto SCID mice, human grafts treated with Ad/VEGF, a replication-deficient adenovirus containing $VEGF_{121}$ cDNA, showed a slower rate of development of epidermal necrosis and epidermal ulcerations as compared to human grafts treated with saline or LacZ, a recombinant virus producing β-galactosidase protein which is used as a control. (page 33, lines 15-25) Therefore, Claims 5 and 6 are anticipated.

Herlyn et al. teach a method for increasing vascular development in mammalian tissue comprising administration of an adenovirus vector wherein the said vector is "suspended in a biologically compatible solution or pharmaceutically acceptable delivery vehicle," such as saline. Therefore, Claim 7 is anticipated.

Herlyn et al. teach a method for increasing vascular development in mammalian tissue comprising administration of an adenovirus vector wherein the method is utilized in both a xenograft preparation comprising human tissue grafts infected with an adenoviral vector expressing growth factor transplanted onto SCID mice (an example of complete dissociation of the tissue) (page 58, lines 2-10) and a wound healing preparation comprising surgical wounding of established human tissue grafts on SCID mice (an example of tissue substantially cut away from surrounding tissue, but connected to animal host) (page 58, line 23 to page 59, line3). In both procedures, human tissue grafts were infected with said adenoviral vector prior to re-association. Therefore, Claims 8-11 are anticipated.

Finally, Herlyn et al. teach a method for increasing vascular development in mammalian tissue comprising administration of a recombinant-deficient adenovirus vector wherein the vector encodes $VEGF_{121}$ and platelet-derived growth factor (PDGF)-B and platelet-derived growth factor (PDGF)-A (see Claims 4 and 5, Herlyn et al.). Wherein PDGF falls within the limitations of Claim 12, which limits a method of increasing vascularity in a tissue flap, the method comprising contacting of tissue flap with an adenoviral vector comprising a nucleic acid sequence encoding acidic fibroblast growth factor, basic fibroblast growth factor, alpha tumor necrosis factor, beta tumor necrosis factor, platelet-derived growth factor, or angiogenin, Claim 12 is anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herlyn et al. (WO 98/39035, published September 11, 1998, filed March 6, 1998) in view of Cockerill et al. (Int Rev Cytol 159:113-60, 1995).

Claim 12 directs to the claimed invention wherein the angiogenic factor being expressed in the adenoviral vector is acidic fibroblast growth factor, basic fibroblast

growth factor, alpha tumor necrosis factor, beta tumor necrosis factor, platelet-derived growth factor, or angiogenin.

Herlyn et al. teach a method for "increasing/inducing vascular development in mammalian tissue by delivering to the tissue a replication defective recombinant virus, preferably adenovirus, comprising a human growth factor gene under the control of regulatory sequences capable of directing expression of that gene in the tissue," (page 6, lines 1-6). While Herlyn et al. specifically uses the growth factors, VEGF and PDGF, in their examples, they disclose the use of this model for "studying the events that occur after the injection of growth factors, such as PDGF, VEGF, TGF-b and insulin-like growth factor, or others," (page 19, lines 2-3) and "screening compounds for the treatment of angiogenic disorders." (page 19, lines 15-16). Herlyn et al. do not teach the use of acidic fibroblast growth factor, basic fibroblast growth factor, alpha tumor necrosis factor, beta tumor necrosis factor, or angiogenin in said method.

Prior art by Cockerill et al. teaches a series of factors that act as enhancers of angiogenesis including alpha and beta tumor necrosis factor, acidic and basic fibroblast growth factor, and angiogenin (pages 133-137) and at the time of the invention, the nucleic acid sequences for these factors were known in the art. For example, gene transfer of acidic fibroblast growth factor was shown to cause neovascularization of the intimal thickening of endothelium (page 135, paragraph 3; page 136, paragraph 1).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the vector of Herlyn et al. by cloning the nucleic acids encoding angiogenic factors and administering such a vector to poorly vascularized mammalian

tissue to induce angiogenesis with a reasonable expectation of success. An artisan would have had a reasonable expectation of success because Herlyn et al. teach a method for increasing vascularity in tissue by administering to the tissue an adenovirus vector comprising a human growth factor gene, specifically PDGF and VEGF, and Cockerill et al. teach that acidic and basic fibroblast growth factor, alpha and beta tumor necrosis factor and angiogenin have been shown to share similar modulatory ability of angiogenesis with VEGF and PDGF. An artisan would have been motivated to modify the method of Herlyn et al. in light of Cockerill et al. to induce angiogenesis in tissue by expressing alternative growth factors using a viral vector because it would be clinically useful to have alternative compounds that can be used in inducing or stimulating vascularity for the treatment or prevention of pathological clinical situations characterized by local hypovascularity such as surgeries, wounds and cardiac ischemia.

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Norma C Alonzo whose telephone number is 571-272-2910. The examiner can normally be reached on 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NCA

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PRIMARY EXAMINER